REMARKS

Claims 27-34 are pending in this application.

In this submission, Applicants present additional references in support of Applicants' arguments. Applicants note that some of the references are provided in the form of full-text articles, while others are provided as abstracts. Applicants submit that the full-text articles are provided solely because they are available, and that Applicants do not intend to make any distinction among the references, or to indicate that some references are more pertinent or material than others.

Applicants respectfully traverse the present rejections.

Rejection under 35 U.S.C. § 101:

Claims 27-34 stand rejected under 35 U.S.C. §101 as allegedly not supported by either an asserted utility that is specific and substantial or by a well-established utility. Specifically, the Office action alleges that because "Applicants have not provided any testing of PRO357 polypeptide expression . . . there is no reason for a skilled artisan to be reasonably convinced that the PRO357 polypeptide will exhibit the asserted diagnostic behavior." Page 3 of the Office action mailed 9/18/06. In the view of the Office, "[t]he correlation between the disclosed amplification of the PRO357 nucleic acid and a change in PRO357 polypeptide expression is unknown and is not disclosed." Page 3 of the Office action mailed 9/18/06.

Applicants respectfully disagree and maintain that claims 27-34 are supported by the specific and substantial utility asserted at page 119 of the specification. More specifically, Applicants maintain that the PRO357 gene amplification correlates with PRO357 polypeptide overexpression and that this is sufficient to confer patentable utility to the instantly claimed PRO357 polypeptides. The Office action rejects Applicants argument that there is a recognized correlation between PRO357 gene amplification and protein overexpression because the specification does not provide explicit evidence that amplification of the PRO357 polynucleotide correlates with overexpression of the PRO357

polypeptide. However, Applicants maintain that explicit evidence is not required to demonstrate an adequate utility. Indeed, according to MPEP § 2107.02, "the applicant does not have to provide evidence . . . such that it establishes an asserted utility as a matter of statistical certainty." Thus, it is not a legal requirement to establish a "necessary" correlation between an increase in PRO357 gene copy number and PRO357 protein expression levels. Instead, as discussed previously, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, if the totality of the evidence demonstrates that it is more likely than not that PRO357 gene amplification correlates with PRO357 polypeptide overexpression, that is sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

It appears that the rejection for lack of utility is based on application of the wrong standard for determining whether an Applicants' assertion of utility is sufficient. Specifically, the Office action applies a standard that "Office personnel [ ] must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." Page 4 of the Office action mailed 9/18/06. Under this standard it appears that a utility rejection is considered proper if ***any*** countervailing evidence is cited. However, that standard is legally incorrect. The proper standard is set forth in the MPEP at Section 2107.02:

> evidence (of utility) will be sufficient if, **considered as a whole**, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

Thus, **the totality of the evidence**, including arguments, declarations, and submitted references **must be considered** and a rejection for lack of utility ***cannot*** *properly be maintained if the totality of that evidence demonstrates that the asserted utility is more likely true than not true.* *See e.g., In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965), *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA

1980), *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967), and *In re Chilowsky*, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956).

According to the Office action, the declarations, including those of Audrey Goddard, Ph.D. and Paul Polakis, Ph.D., and references by Pollack, Orntoft, Hyman, Bermont, Varis, Hu, Papotti, Walmer, Janssens, Hahnel, Kammori, Bea, Maruyama, and Futcher, "only show that it is not implausible that (the) invention will work for its intended purpose." Page 4 of the Office action mailed 9/18/06. Under the utility standard applied by the Office, such a showing is insufficient to support Applicants' assertion of utility. Applicants however, respectfully disagree. Applicants submit that when the evidence is considered in its entirety, **as it must be**, it is clear that a correlation between PRO357 gene amplification and protein overexpression must be acknowledged.

Indeed, while Applicants acknowledge that there may be some instances where gene amplification does not correlate with protein overexpression (even the Scott Declaration acknowledges this point), Applicants respectfully maintain that absolute certainty is not required. Specifically, statistical certainty regarding an Applicants' assertion of utility is not required to satisfy 35 U.S.C. § 101. *Nelson v. Bowler,* 626 F.2d 853, 856-857, 205 USPQ 881, 883-884 (CCPA 1980). Moreover, where an Applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed as "wrong" even where there may be some reason to question the assertion. MPEP § 2107.02. Rather, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. *In re Gazave,* 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (emphasis added).

Thus, even if Pennica and Konopka, which are relied on by the Office action as "countervailing evidence," provide evidence of some instances where gene amplification does not correlate with protein overexpression these references alone do not demonstrate that the asserted utility violates a scientific principle, is wholly inconsistent with contemporary knowledge in the art, or make it more likely than not that a correlation between gene amplification and protein overexpression does not exist. Indeed, this is

particularly true when the evidence is considered in its totality, as it must be. Specifically, the ample evidence submitted and relied on by Applicants, including the Scott (discussed at pages 9-10), Polakis, and Goddard Declarations, and the numerous references discussed in the responses submitted 10/17/2005 and 6/12/2006, including Pollack, Orntoft, Hyman, Bermont, Varis, Hu, Papotti, Walmer, Janssens, Hahnel, Kammori, Bea, Maruyama, and Futcher, as well as the references discussed herein, including Wang, Munaut, Hui, Khal, Caberlotto, Misrachi and Shemesh, Stein, Gou and Xie, Godbout, Van der Wilt, Grenback, Shen, and Fu, clearly demonstrates that instances when gene amplification does not correlate with protein overexpression are the exception and not the rule. The declarations submitted by and references cited by Applicants clearly establish that the contemporary knowledge in the art agrees with the scientific principle that gene amplification correlates with protein overexpression.

According to the Office action, "Pennica is evidence that not all gene amplifications are associated with overexpression of the corresponding gene product and that the skilled artisan would not have appreciated that PRO357 gene amplification, without more, would have suggested a specific and substantial patentable utility for the PRO357 polypeptide and antibodies thereto." Page 6 of the Office action mailed 9/18/06.

Applicants respectfully disagree. Although Pennica may illustrate that increased copy number does not *necessarily* result in increased polypeptide expression, Pennica *et al.* does not teach that no correlation can be presumed. Moreover, as stated above, the standard for determining whether a correlation can be presumed is not absolute certainty. Rather, Applicants only must show that the existence of a correlation between gene amplification and protein overexpression is generally more likely than not. The fact that in Pennica, a case focused on a specific class of closely related molecules, there seemed to be no correlation with gene amplification and the level of mRNA/protein expression for one of the genes examined does not establish that it is more likely than not, in general, that such correlation does not exist. The Office action fails to show whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, as illustrated by the Scott and Polakis Declarations and the

references previously cited by Applicants, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. *See, e.g.* Second Declaration of Paul Polakis. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . ." (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added).

The Office action also questions Applicants' argument distinguishing Pennica, *i.e.* that "it is possible that the apparent amplification observed for *WISP-2* (in Pennica) may be caused by another gene in this amplicon." Page 6 of the Office action mailed 9/18/06. The Office action states that if this is correct, then it may be true that the gene amplification in the present application may fail to satisfy the utility requirements of 35 U.S.C. § 101 for the PRO357 polypeptide and polynucleotide. Page 6 of the Office action mailed 9/18/06.

Applicants respectfully disagree. The Office action misinterprets Applicants' argument, which is based on statements in Pennica itself. Specifically, Applicants' argument that *WISP-2* results reported by Pennica should be disregarded because the observed amplification might be caused by another gene comes directly from Pennica's characterization of the *WISP-2* gene amplification data:

> *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. The gene for human *WISP-2* was localized to chromosome 20q12-20q13, at a region frequently amplified and associated with poor prognosis in node negative breast cancer and many colon cancers, suggesting the existence of one or more oncogenes at this locus (36-38). Because the center of the 20q13 amplicon has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon.

Pennica *et al* "*WISP* genes are members of the connective tissue growth factor family that are up-regulated in WNT-1 transformed cells and aberrantly expressed in human colon tumors." 1998. *PNAS:* 95:14717-14722, 14722. In contrast, Applicants teach in the specification that the procedures used for confirming amplification in the present invention

strongly indicate that the "DNAs tested are responsible for the amplification of the particular region on the respective chromosome." Page 137, lines 13-20 of the specification. *See also* pages 134-137 of the specification for specific procedures used to confirm amplification of PRO357 DNAs, including epicenter mapping. Thus, the demonstrated gene amplification in the present specification does not fail to satisfy the utility requirement for any of the PRO357 polynucleotides, polypeptides, or antibodies.

Moreover, Applicants maintain that, for the reasons provided in the previous responses, a correlation between gene (DNA) amplification and elevated protein levels exists, in general. In addition, in his declaration submitted with the Amendment and Request for Reconsideration mailed October 17, 2005 Dr. Polakis states that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on his own factual findings.

Applicants further presented a second Declaration by Dr. Polakis (Polakis II) with evidentiary data in Exhibit B (response of June 12, 2006). Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis provides facts to enable the Examiner to draw independent conclusions regarding protein data.

Applicants further enclose a Declaration by Dr. Randy Scott. Dr. Scott was a co-founder of Incyte Pharmaceuticals, Inc., the world's first genomic information business, and is currently the Chairman and Chief Executive Officer of Genomic Health, Inc., a life science company located in Redwood City, California, which provides individualized

information on the likelihood of disease recurrence and response to certain types of therapy using gene expression profiling. Based on his more than 15 years of personal experience with the DNA microarray technique and its various uses in the diagnostic and therapeutic fields, and his familiarity with the relevant art, Dr. Scott unequivocally confirms that, as a general rule, there is a good correlation between mRNA and protein levels in a particular tissue. As stated in paragraph 10 of the Scott Declaration:

> "One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, **it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue**. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, **without the need to directly measure individual protein expression levels.**" (emphasis added).

The conclusions of the Polakis I and II, and the Scott Declarations are further supported by the teachings within Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (herein after Cell 3rd) and (4th ed. 2002) (excerpts attached as Exhibit 1). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (Emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (Emphasis added). Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (Emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (copy enclosed in Exhibit 1). Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" *Zhigang* at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." *Zhigang* at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state

that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7

Further, Meric *et al.*, Molecular Cancer Therapeutics, Vol. 1, 971-979 (2002) (a copy enclosed in Exhibit 1) states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (Emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the Declarations of Dr. Polakis and Dr. Scott, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

In addition to the supporting references previously submitted, Applicants submit herewith further references as additional support for their assertion that, changes in DNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

For example, in a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 2) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors

state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 3) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 4) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 5) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20S alpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 6). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 7) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of

bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 8), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, *e.g.,* a decrease, lead to a corresponding change in the level of the encoded protein, *e.g.,* a decrease.

In an article by Guo and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 9) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome (ARDS) by examining the expression of MIF mRNA and protein in lung or colon tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lung or colons. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lung or colons." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular

gene, *e.g.,* an increase, generally leads to a corresponding change in the level of protein expression, *e.g.,* an increase.

In addition to these supporting references, Applicants also submit herewith additional references which offer support of Applicants' asserted utility. For example, in a study which is closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 10) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 11) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 12) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 13) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression

level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 14) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases). " *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith approximately 100 additional references (attached as Exhibit 15) which also support Applicants' assertion in that they report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of more than 140 references, in addition to the declarations and references already of record, to support Applicants' asserted utility. These references support the assertion that in general, a change in DNA levels for a particular gene leads to a corresponding change in the protein levels. As Applicants have previously acknowledged, the correlation between changes in DNA levels and protein levels is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in DNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

The Office action also asserts that even if PRO357 gene amplification correlates with PRO357 polypeptide overexpression, the claims still are not supported by an adequate utility because one of ordinary skill in the art would not know how to use the claimed antibodies in a practical way. Specifically, the Office action accepts, for the sake of argument, "that a person skilled in the art could derive some data regarding PRO357 polypeptide expression in tumors in which the PRO357 polynucleotide is amplified," and "that such data could be used to correlate PRO357 polypeptide expression with PRO357 polynucleotide amplification." Page 8 of the Office action mailed 9/18/06. However, the Office action alleges that even accepting these arguments, the utility requirement is not satisfied because "the specification provides no guidance to enable the skilled artisan to use data relating to PRO357 polypeptide expression in any practical way." Page 8 of the Office action mailed 9/18/06.

Applicants respectfully disagree. Specifically, at page 137 of the specification, Applicants explain that "[b]ecause amplification of the DNAs tested occurs in various lung and colon tumors, it is highly probable that these DNAs play a significant role in tumor formation or growth. As a result . . . [t]he polypeptides encoded by the DNAs tested have utility as diagnostic markers for determining the presence of tumor cells in lung and/or colon tissue samples." Additionally, at page 119, the specification asserts that "[a]mplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers. . . . These amplifications also are useful as diagnostic markers for the presence of a specific type of tumor type." Thus, the specification does provide guidance for how the skilled artisan would use the data relating to PRO357 polypeptide expression in a practical way.

Further, the example provided in the Office action does not alter this. Specifically, the Office action posits that if PRO357 polypeptide were shown to be overexpressed in tissues where the PRO357 nucleic acid is not amplified, a skilled worked would not be enabled by the specification to use that information in any meaningful way. Applicants respectfully disagree that such a situation demonstrates the claimed invention is not supported by an adequate utility. As discussed above, the asserted utility for the claimed polypeptides and

antibodies is based on an art acknowledged correlation between gene amplification and protein overexpression. Indeed, even the Office action accepts, "for the sake of argument," that such a correlation exists. The specification teaches that a polypeptide encoded by a gene amplified in cancerous tissues is useful as a therapeutic or diagnostic agent. The example provided in the Office action assumes a different set of facts. Specifically, it assumes that the polypeptide overexpression does not correlate with gene amplification. Such a relationship may or may not provide a utility sufficient to satisfy 35 U.S.C. § 101. However, that is irrelevant, because only a single utility is required and that utility is demonstrated by the correlation between gene amplification and protein overexpression. *See* MPEP § 2107.

Further, although Applicants disagree with the Office action's rejection of the Ashkenazi Declaration and characterization of the teachings of the Hanna reference, *see e.g.* Page 7 of the Office action mailed 9/18/06, Applicants respectfully submit that they need not rely this additional utility to support the claimed invention. As stated above, MPEP § 2107 requires only "<u>one</u> credible assertion of a specific and substantial utility for each claimed invention to satisfy the utility requirement." (Emphasis added)). Applicants respectfully submit that the diagnostic (or therapeutic) utility of PRO357 polypeptides and antibodies is adequately asserted and supported by the substantial evidence discussed herein, which demonstrates that in general it is more likely than not likely that gene amplification correlates with protein overexpression. The utility requirement of 35 U.S.C. § 101 does not require that this correlation be observed all the time or in all instances. Rather, 35 U.S.C. § 101 only requires that the correlation more likely exists than not exists. The Office has not provided evidence that outweighs the evidence submitted by Applicants, including declarations and reference articles, showing that more likely than not gene amplification correlates with protein overexpression.

For the reasons given above, Applicants respectfully submit that consideration of the totality of the evidence clearly demonstrates that Applicants' asserted utility is specific, substantial, and credible. Applicants have overcome this ground of rejection and respectfully request it be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph:

Enablement

The Examiner contends that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. Applicants respectfully disagree. As discussed above, the claimed invention is adequately supported by an asserted utility that is both specific and substantial. Applicants respectfully request the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112 ¶1 for alleged inadequate disclosure on how to use the claimed invention.

Claim Rejections under 35 U.S.C. § 102(b)

The Office action rejects claims 27-34 under 35 U.S.C. § 102(b) as being anticipated by Botstein *et al.* (WO 99/35170, published 7/15/99). Anticipation under 35 U.S.C. § 102(b) requires that "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, *more than one year prior to the date of application for patent in the United States.*"

An application for a patent based on the present invention was filed at least as early as December 22, 1998, which is prior to the publication date of the cited reference. In particular, the PRO357 polypeptide and amino acid sequences are disclosed in U.S. Provisional Application Serial No. 60/113,296 ("the '296 application"), filed 12/22/1998. More specifically, the nucleic acid sequence encoding PRO357 is identified as DNA44804 and is shown in Figure 15 (SEQ ID NO:15) of the '296 application. This sequence corresponds to Figure 25 (SEQ ID NO:68) in the present application. The amino acid sequence encoding PRO357 is shown in Figure 16 (SEQ ID NO:16) of the '296 application, which corresponds to Figure 26 (SEQ ID NO:69) in the present application. In addition, the gene amplification experiment described in Example 28 of the present specification is described in Example 2 of the '296 application. For the reasons discussed above, description of the gene amplification assay in the '296 application satisfies the utility and enablement requirements.

As an application for a patent based on the present invention was filed at least as early as December 22, 1998, Applicants respectfully submit that rejection of claims 27-34 under 35 U.S.C. § 102(b) based on the Botstein reference (WO 99/3517, published 7/15/99) is improper and respectfully request that this ground of rejection be withdrawn.

CONCLUSION

Applicants believe this Request for Reconsideration fully responds to the Office Action. Applicants respectfully request the Examiner grant allowance of claims 27-34. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite this application.

Applicants believe no fee is due in connection with the filing of this Request for Reconsideration, however, should any fees be deemed necessary for any reason relating to this paper, the Commissioner is hereby authorized to deduct said fees from Brinks Hofer Gilson & Lione Deposit Account No. 23-1925. A duplicate copy of this document is enclosed.

Respectfully submitted,

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